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(12) # EUROPEAN PATENT SPECIFICATION

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EP-A-0 054 974
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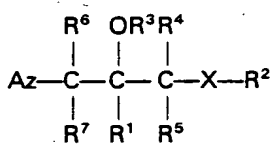
Description

This invention relates to novel triazole derivatives which have antifungal activity and are useful in the treatment of fungal infections in humans.

In particular the invention relates to certain 3-heterocyclylmethylthio- and 3-arylmethylthio-1-triazolyl-2-propanol derivatives which are particularly effective as oral and topical agents for the treatment of fungal diseases in humans and other animals, and to pharmaceutical compositions containing such compounds.

EP—A—0061835 discloses a broad class of triazole and imidazole compounds having the general formula:

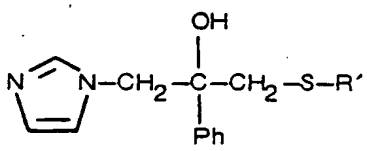


(A)

wherein R^1 and R^2, which may be the same or different, are hydrogen, alkyl, optionally substituted cycloalkyl, cycloalkylmethyl, alkenyl, heterocyclyl, aryl or aralkyl optionally substituted with halogen, nitro, alkyl, haloalkyl, alkoxy, phenyl, phenoxy, benzyl, benzyloxy, halophenyl or haloalkoxy; R^3 is hydrogen, alkyl, alkenyl, alkynyl, aralkyl or acyl; R^4 and R^5, which may be the same or different are hydrogen, alkyl, alkenyl or optionally substituted aryl; R^6 and R^7, which may be the same or different are hydrogen, alkyl, alkenyl or optionally substituted aryl; X is oxygen or sulphur or is SO or SO_2 and Az is a 1,2,4- or 1,3,4-triazole or imidazole ring; and isomers, acid addition salts and metal complexes thereof.

The compounds are stated to possess fungicidal activity, principally as plant fungicides, and also to be plant growth regulators. There is also a brief reference that the compounds are useful for the treatment of candidiasis and human dermatophyte infections.

EP—A—0 054 974 disloses antifungal imidazol compounds of the general formula:



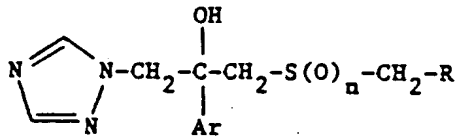
(13)

wherein Ph denotes phenyl or halogenated phenyl and R^1 may e.g. be benzyl.

We have discovered that a particular class of non-exemplified compounds within formula (A) wherein R^3, R^4, R^5, R^6 and R^7 are H, X is S or SO and R^2 is arylmethyl are surprisingly particularly effective as human antifungal agents and this property is not shared by the compounds wherein R^2 is aryl, which are the only compounds where X is S exemplified in EP—A—0 061 835.

The invention also includes corresponding heterocyclomethyl derivatives which are not within the scope of EP—A—0 061, 835.

Thus according to the invention, there are provided compounds of the formula:



---(I)

wherein

Ar is phenyl substituted by from 1 to 3 substituents each substituent being independently halo or CF_3;

n is 0 or 1; and

R is a phenyl or a phenyl group substituted by from 1 to 3 substituents, each substituent being independently halo, CF_3, C_2—C_4 alkoxy, C_2—C_5 alkoxycarbonyl or C_1—C_4 alkylthio; or a 5 or 6 membered aromatic heterocyclic group linked via a ring carbon atom and optionally substitued by one or more halo, CF_3, C_1—C_4 alkyl, C_1—C_4 alkoxy, amino, mono or di-(C_1—C_4 alkyl) amino, C_2—C_5 alkanoylamino, hydroxy or thio groups, and salt forms thereof.

"Halo" means F, Cl, Br or I.

Particular examples of heterocyclic groups include 2-imidazolyl, 4-thiazolyl, 3-thienyl, 2-furyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, 2-(1,3,4-thiadiazolyl), 2-, 3- and 4-pyridyl and 2- and 4-pyrimidinyl, each of which may be substituted as previously defined.

Alkyl, alkoxy and alkanoyl groups may be straight or branched chain where appropriate.

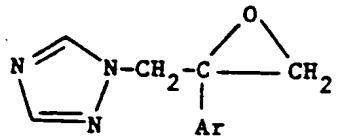
The invention also provides a pharmaceutical composition comprising a compound of the formula (I) or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use in treating fungal infections in animals, including humans.

A preferred substituted phenyl group for Ar is halo or dihalophenyl, especially 2,4-dichlorophenyl.
n is preferably 0.
R is preferably a 2-pyridyl, 1-methyl-2-imidazolyl, 2-amino-4-thiazolyl or 1-methyl-5-tetrazolyl group.
Particularly preferred individual compounds of the invention include:
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-pyridylmethylthio)propyl]1,2,4-triazole,
1-[2-2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-2-imidazolylmethylthio)propyl]1,2,4-triazole,
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-amino-4-thiazolylmethylthio)propyl]1,2,4-triazole, and
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-5-tetrazolylmethylthio)propyl]1,2,4-triazole.

The compound of formula (I) can be obtained by a number of different processes according to the invention.

1. In one process, the compounds of the formula (I) in which n is 0 can be prepared from an oxirane of the formula:



--- (II)

by reaction with a thiol of the formula:

III

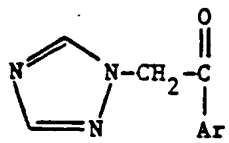
wherein Ar and R are as previously defined.

The reaction can be achieved under a variety of different conditions, depending to some extent on the precise nature of the reactants. Generally it is possible to achieve the reaction in a convenient manner by simply heating the oxirane (II), as its free base, with excess of the thiol (III) in an organic solvent, (e.g. dioxan. A period of up to three days at reflux temperature is generally sufficient, however addition of a catalytic amount of dilute sodium hydroxide solution often gives improved yields and reduces reaction times. The product can be isolated and purified by conventional procedures, for example by evaporating the solvent, taking the product up in a water-immiscible organic solvent, extracting the solution with dilute sodium hydroxide or potassium carbonate solution to remove unreacted thiol, drying and evaporating the solvent. The product may be further purified, if desired, by crystallisation or by chromatography.

As an alternative procedure, the oxirane as its methanesulphonate salt and the thiol are heated together in an organic solvent, e.g. N,N-dimethylformamide or tetrahydrofuran, in the presence of a base, e.g. potassium carbonate or sodium hydride. A temperature of from 60 to 80°C is generally employed, and under these conditions the reaction is generally substantially complete within a few hours. The product is isolated and purified as previously described.

As a further variation the oxirane as its methanesulphonate salt is heated with excess of the heterocyclic thiol under reflux in glacial acetic acid for a period of several hours.

The oxiranes (II) can be obtained by conventional methods, typically from the corresponding ketones (IV):



--- (IV)

by reaction with dimethyloxosulphonium methylide prepared from trimethylsulphoxonium iodide and either sodium hydride in dimethylsulphoxide or using cetrimide and sodium hydroxide in a mixture of water and toluene.

The reaction using sodium hydride is typically achieved by adding dry powdered trimethylsulphoxonium iodide to a suspension of sodium hydride in dimethylsulphoxide. After stirring for 30 minutes at room temperature, the ketone (IV) is added in an approximately equimolar amount in dimethylsulphoxide. The reaction mixture may be warmed to accelerate the reaction and after several hours at 50°—80°C, the product can be isolated by conventional procedures.

The reaction utilising certimide is typically achieved by stirring the ketone (IV), trimethylsulphoxonium iodide and cetrimide vigorously together in a mixture of toluene and sodium hydroxide solution for about an hour at up to about 100°C. The oxirane product can then be isolated by conventional procedures.

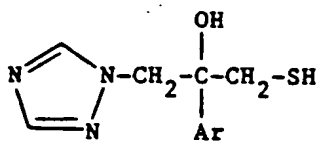
When Ar is a phenyl group containing no ortho substituent the cetrimide route should be used.

The ketones (IV) are either known compounds or can be prepared by procedures analogous to those of the prior art. The preparation of 2 - (1H - 1,2,4 - triazol - 1 - yl) - 2' - 4' - dichloroacetophenone from 2 - bromo - 2',4' - dichloroacetophenone, 1,2,4-triazole and potassium carbonate is, for example, described in Example 1 of British Patent Specification No. 1512918, which utilises acetonitrile as the solvent under reflux

for 20 hours. We have found that this type of reaction is generally best carried out in acetone at 0—20°C, when it is generally complete in a shorter period of time, e.g. 4 hours or less.

The thiols of formula III are generally known compounds or they are prepared from readily available starting materials by conventional reactions.

2. In an alternative synthesis the compounds of the formula (I) where n is 0 may be prepared from a thiol of formula:



--- (V)

by reacting with a halide of the formula:

$$X—CH_2—R \qquad (VI)$$

wherein Ar and R are as previously defined and X is chloro, bromo or iodo. The reaction is generally carried out by stirring the reactants together in an inert organic solvent, e.g. N,N-dimethylformamide, in the presence of a base. e.g. NaOH or K_2CO_3. A period of a few hours at room temperature is generally sufficient, but if necessary the reaction mixture can be heated to accelerate the reaction. The product can be isolated and purified by conventional procedures.

The thiols of formula (V) may be prepared from the oxiranes of formula (II) by first reacting with a thiolacetic acid and then deacylating the resulting product e.g. using sodium ethoxide in ethanol followed by acidification with hydrochloric acid.

The halides of formula (VI) are generally known compounds or they may be prepared by conventional procedures in accordance with literature precedents.

3. The compounds of the formula (I) in which n is 1 (sulphoxides) can be prepared by the controlled oxidation, of the corresponding compounds in which n is 0.

The preferred oxidizing agent is *m*-chloroperbenzoic acid: approximately one equivalent should be used to prepare the sulphoxides.

In a typical procedure the thio ocmpound is dissolved in a mixture of isopropanol and chloroform (1:1, v/v) and the solution is cooled to below 5°C in an ice bath. Slightly less than 1 equivalent of *m*-chloroperbenzoic acid is added in portions over a few minutes. The mixture is then stirred for about two hours. If thin layer chromatography indicates unreacted starting material, a further small quantity of *m*-chloroperbenzoic acid (up to a total of 1 equivalent) is added. The sulphoxides have two asymmetric centres and thus exist in two diastereoisomeric forms. Thus the sulphoxide product of the oxidation, which can be isolated by conventional procedures, will be a mixture of the two diastereoisomers. If desired, the diastereoisomers can be separated by column chromatography, e.g. on silica, since they usually differ in polarity.

4. In the case where the heterocyclic ring contain substituted groups, conventional chemical transformation reactions can be used to prepare simple derivatives and related compounds.

Thus for example when the heterocyclic ring contains an amino group, a conventional acetylation reaction (e.g. using acetic anhydride in pyridine) may be employed to prepare the N-acetyl derivative. Other transformation reactions and the reagents and conditions required for their performance will be well known to those skilled in the art.

All the compounds of the invention contain at least one chiral centre, and the invention includes both resolved and unresolved forms.

For pharmaceutical use, acceptable acid addition salts of the compounds of the formula (I) include those formed from strong acids which form non-toxic acid addition salts, such as hydrochloric, hydrobromic, sulphuric, nitric, oxalic and methanesulphonic acids.

The salts may be obtained by conventional procedures, e.g. by mixing solutions containing equimolar amounts of the free base and desired acid, and the required salt is collected by filtration, if insoluble, or by evaporation of the solvent.

The compounds of the formula (I) and their pharmaceutically acceptable salts are anti-fungal agents, useful in combating fungal infections in animals, including humans. For example they are useful in treating topical fungal infections in man caused by, among other organisms, species of *Candida, Trichophyton, Microsporum,* or *Epidermophyton*, or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They may also be used in the treatment of systemic fungal infections caused by, for example, *Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Coccidioides, Paracoccioides, Histoplasma* or *Blastomyces.*

The *in vitro* evaluation of the anti-fungal activity of the compounds can be performed by determining the minimum inhibitory concentration (m.i.c.) of the test compounds in a suitable medium at which growth of the particular micro-organism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration are inoculated with a standard culture of, for

example, *Candida albicans* and each plate is then incubated for 48 hours at 37°C. The plates are then examined for the presence of growth of the fungus and the appropriate m.i.c. value is noted. Other micro-organisms used in such tests can include *Cryptococcus neoformans, Aspergillus fumigatus, Trichophyton* spp; *Microsporum* spp; *Epidermophyton floccosum, Coccidioides immitis*, and *Torulopsis glabrata.*

The *in vivo* evaluation of the compounds can be carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice which are inoculated with a strain of *Candida albicans*. Activity is based on the survival of a treated group of mice after the death of an untreated group of mice following 48 hours observation. The dose level at which the compound provides 50% protection against the lethal effect of the infection is noted.

For human use, the anti-fungal compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients, the daily dosage level of the anti-fungal compounds of the formula (I) is from 0.1 to 10 mg/kg (in divided doses) when administered by either the oral or parenteral route. Thus tablets or capsules of the compounds contain from 5 mg to 0.5 g of active compound for administration singly or two or more at a time as appropriate. In any event the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the anti-fungal compounds of formula (I) may be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they may be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they may be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The compounds of the invention also have activity against a variety of plant pathogenic fungi, including for example various rusts, mildews and moulds, and the compounds are thus useful for treating plants and seeds to eradicate or prevent such diseases.

The following Examples illustrate the invention:

Example 1

1-[-3-(4-Chlorobenzylthio)-2-(2,4-dichlorophenyl)-2-hydroxypropyl]-1,2,4-triazole

2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)oxirane methanesulphonate salt (0.336 g, 1 mmole), 4-chlorobenzyl mercaptan, (0.159 g, 1 mmole) and anhydrous potassium carbonate (0.414 g, 3 mmole) were stirred in dry N,N-dimethylformamide (15 ml) at 70°C for 72 hours. The reaction mixture was diluted with water (70 ml) and extracted with ethyl acetate (2 × 70 ml). The extracts were combined and evaporated to give an oil which crystallised on standing. Recrystallisation from a mixture of ethyl acetate and n-hexane gave the title compound (0.23 g, 53%) m.p. 106—107°C.

Analysis %:

Found:	C, 50.74;	H, 3.56;	N, 10.14
$C_{18}H_{16}Cl_3N_3OS$ requires:	C, 50.42;	H, 3.76;	N, 9.80

Example 2

1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-pyridylmethylthio)propyl]-1,2,4-triazole

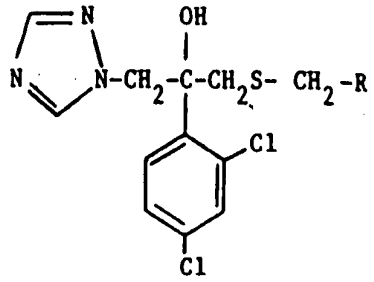
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-mercaptopropyl-1,2,4-triazole (0.5 g, 1.64 mmole) and anhydrous potassium carbonate (0.69 g, 5 mmole) were stirred together in N,N-dimethylformamide (10 ml) and the mixture was cooled in ice 2-Chloromethylpyridine hydrochloride (0.3 g, 1.83 mmole) was added and stirring in ice was continued for a further 1 hour. The reaction mixture was then poured into a mixture of dichloromethane (50 ml) and water (50 ml) and the organic layer was separated. The aqueous layer was extracted a further 5 times with dichloromethane (50 mls in total) and the combined organic extracts were dried over magnesium sulphate and evaporated. The residue was chromatographed on silica, eluting with a mixture of dichloromethane and methanol (97:3), to give the title compound as a colourless gum (0.58 g, 90%). Treatment of the product with ethereal hydrogen chloride gave the dihydrochloride monohydrate as a hygroscopic white solid, m.p. 136—141°C.

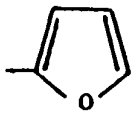
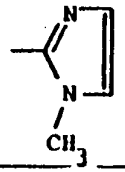
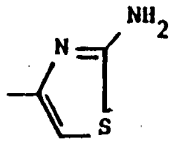
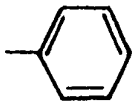
Analysis %:

Found:	C, 41.97;	H, 3.92;	N, 11.68
$C_{17}H_{20}Cl_4N_4O_2S$ requires:	C, 41.98;	H, 4.11;	N, 11.5

Examples 3—10

The following compounds were prepared by the general procedures described in Examples 1 and 2 using the appropriate starting materials.



Example No.	R	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
3		56-60	46.00 (45.58	3.69 3.61	8.52 8.86)
4		115-17	48.2 (48.28	4.27 4.39	17.59 17.99)
5		151-6	43.25 (43.27	3.62 3.61	17.23 16.83)
6		52-4 (c)	49.56 (49.60	4.16 3.95	8.36 8.68)

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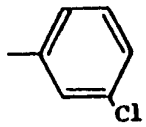
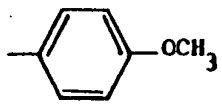
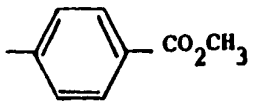
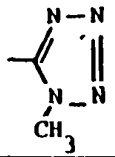
Example No.	R	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
7		134-6 (b)	46.10 (46.47	3.70 3.68	9.26 9.03)
8		124-6 (b)	49.12 (49.52	4.44 4.37	8.96 9.12)
9		102-5 (c)	49.46 (48.72	4.15 3.90	7.54 7.75)
10		155-156.5	42.16 (42.0	3.86 3.75	24.63 24.5)

(a) dihydrochloride, monhydrate
(b) monohydrochloride
(c) monooxalate

Example 11

1-[3-(4-Chlorobenzylsulphinyl)-2-(2,4-Dichlorophenyl)-2-hydroxypropyl]-1,2,4-triazole

1 - [3 - (4 - Chlorobenzylthio - 2 - (2,4 - dichlorophenyl) - 2 - hydroxypropyl]1,2,4 - triazole (2.15 g, 5 mmole) was dissolved in a mixture of dichloromethane (30 ml) and isopropanol (30 ml). The solution was stirred and cooled in ice. To this solution was added meta-chloroperbenzoic acid (85% pure; 1.02 g, 5 mmole) in three portions over a period of five minutes. The reaction was allowed to proceed for 24 hours at room temperature. Dichloromethane (100 ml) was added and the organic layer separated and washed twice with a solution of sodium carbonate (2.5 g) and sodium metabisulphite (2.5 g) in water (100 ml). The organic layer was then dried over magnesium sulphate and evaporated to give a mixture of the two sulphoxide diastereomers as an oil which crystallised on standing. Recrystallisation from ethyl acetate gave the title compound as a single pure isomer (t.l.c.: Rf 0.30; silica; ethyl acetate, methanol, ammonium hydroxide, 90:10:1) (0.34 g, 15%) m.p. 193—195°C.

Analysis %:

Found:	C, 48.58;	H, 3.63;	N, 9.44
$C_{18}H_{18}Cl_3N_3O_2S$ requires:	C, 48.61;	H, 3.63;	N, 9.45

The residual mixture obtained by evaporation of the mother liquors was chromatographed on silica eluting with a mixture of ethyl acetate, methanol and concentrated ammonium hydroxide (90:10:1). The relevant fractions were combined and evaporated to give the second isomer (t.l.c.: Rf 0.20; silica; ethyl acetate; methanol; ammonium hydroxide, 90:10:1) which was recrystallised from ethyl acetate (0.25 g, 12%) m.p. 191—193°C.

Analysis %:

Found:	C, 48.75;	H, 3.70;	N, 9.44
$C_{18}H_{16}Cl_3N_3O_2S$ requires:	C, 48.61;	H, 3.63;	H, 9.45

Example 12

The following illustrate pharmaceutical compositions for the treatment of fungal infections.

(1) *Capsule*: 71 parts by weight of the compound of Example 1 are granulated with 3 parts maize starch and 22 parts lactose and then a further 3 parts of maize starch and 1 part magnesium stearate are added. The mixture is regranulated and filled into hard gelatin capsules.

(2) *Cream*: 2 parts by weight of the compound of Example 1 are dissolved in 10 parts of propylene glycol and mixed into 88 parts of a vanishing cream base.

(3) *Pessary*: 2 parts by weight of the compound of Example 1 are suspended in 98 parts of a warm liquified suppository base which is poured into moulds and allowed to solidify.

Preparation 1

Preparation of 2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-oxirane

Sodium hydride (3.78 g, 0.079 mole as 50% dispersion in oil) was suspended, with stirring, in 20 ml of dry diethyl ether. The ether was then removed by decantation, and the sodium hydride was dried in a stream of dry nitrogen. 100 ml of dry dimethyl sulphoxide was added followed by 17.34 g (0.079 mole) of dry powdered trimethylsulphoxonium iodide, in portions, over 15 minutes. The resulting mixture was stirred for 30 minutes at room temperature (20°C). 2 - (1H-1,2,4-Triazol-1-yl)-2',4'dichloro acetophenone (18.33 g, 0.072 mole) as a solution in 50 ml of dry dimethyl sulphoxide was then added. The mixture was heated at 60°C for 3 hours and allowed to stand at room temperature overnight. The reaction mixture was cooled and quenched in ice and the product was then extracted into ethyl acetate (600 ml). The ethyl acetate layer was separated, dried over magnesium sulphate, and concentrated to give a red gum. Column chromatography of the gum on silica, eluting with ether, gave 6.62 g (34.4%) of the title compound as a gum.

Preparation 2

Preparation of 1-[2-(2,4-dichlorophenyl)-2-hydroxy-3-mercaptopropyl]-1H-1,2,4-triazole

2 - (2,4 - Dichlorophenyl)2 - (1H - 1,2,4 - triazol - 1 - ylmethyl) - oxirane 5 g (0.0185 mole) was heated under mild reflux in thiolacetic acid (CH_3COSH) (5 ml) for three hours. The mixture was then cooled and added to a mixture of ice-cooled saturated sodium bicarbonate solution (200 ml) and ethyl acetate (200 ml) and the aqueous layer was separated. The organic layer was washed a further four times with ice cooled saturated sodium bicarbonate solution (200 ml in total), dried over magnesium sulphate and evaporated to give a red gum which was dissolved in ethanol (20 ml). This solution was added dropwise over 15 minutes to a stirred and ice-cooled solution of sodium ethoxide (3.78 g, 0.0556 mole) in ethanol (100 ml). After one hour the mixture was poured into 1N hydrochloric acid (100 ml) and this solution was then neutralised by addition of solid sodium bicarbonate. Extraction with dichloromethane (6 × 50 ml), drying over magnesium sulphate, and evaporation of the combined extracts gave a gum which was

chromatographed on silica, eluting with ethyl acetate, to give after one recrystallisation from ethyl acetate/hexane the title compound, yield 2.3 g, m.p., 139—142.5°C.

Analysis %:

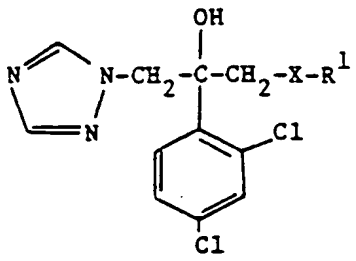
Found:	C, 43.3;	H, 3.7;	N, 14.0
Calculated for $C_{11}H_{11}Cl_2N_3OS$:	C, 43.4;	H, 3.6;	N, 13.8

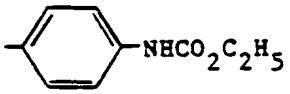
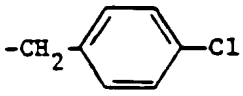
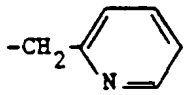
TEST RESULTS

(a) The compounds of the Examples were tested *in vivo* by administration to mice according to the procedures described herein. The dose levels providing 50% protection (PD_{50}) were as follows:

Example No.	PD_{50} (mg/kg)
1	0.8 (i.v.)
2	0.4 (p.o.)
3	2.2 (p.o.)
4	0.2 (p.o.)
5	0.9 (p.o.)
6	1.5 (p.o.)
7	2.2 (p.o.)
8	2.2 (p.o.)
9	1.5 (p.o.)
10	0.6 (p.o.)
11	4.4 (p.o.)

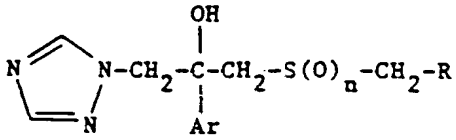
(b) Comparative test results were obtained for the following compounds:



X	R^1	PD_{50} mg/kg
-S-		> 10 (p.o.)
-S-		> 10 (p.o.)
-SO-		> 10 (p.o.)
-O-		> 5 (p.o.)
-O-		> 20 (p.o.)

Claims

1. A compound of the general formula:



---(I)

wherein

Ar is phenyl substituted by from 1 to 3 substituents each substituent being independently halo or CF_3;

n is 0 or 1; and

R is phenyl or henyl group substituted by from 1 to 3 substituents, each substituent being independently halo, CF_3, C_2—C_4 alkoxy, C_2—C_5 alkoxy-carbonyl or C_1—C_4 alkylthio; or a 5 or 6 membered aromatic heterocyclic group linked via a ring carbon atom and optionally substituted by one or more halo, CF_3,

C_1—C_4 alkyl, C_1—C_4 alkoxy, amino, mono- or di-(C_1—C_4 alkyl) amino, C_2—C_5 alkanoylamino, hydroxy or thio groups,
and salt forms thereof.

2. A compound according to claim 1 wherein Ar is mono- or dihalophenyl.

3. A compound according to claim 2 wherein Ar is 2,4-dichlorophenyl.

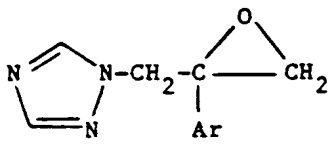
4. A compound according to any one of claims 1 to 3 wherein n is 0.

5. A compound according to claim 1 wherein R is a 2-pyridyl, 1-methyl-2-imidazolyl, 2-amino-4-thiazolyl or 1-methyl-5-tetrazolyl group.

6. A compound according to claim 1 wherein said compound is:
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-pyridylmethylthio)propyl]-1,2,4-triazole,
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-2-imidazolylmethylthio)propyl]-1,2,4-triazole,
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-amino-4-thiazolylmethylthio)propyl]-1,2,4-triazole, and
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-5-tetrazolylmethylthio)propyl]-1,2,4-triazole.

7. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

8. A process for preparing a compound of the formula (I) as claimed in claim 1 which comprises:
(a) reacting a compound of the formula:

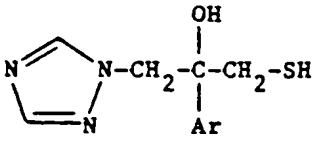


--- (II)

with a thiol of the formula:

$$R—CH_2—SH \qquad (III)$$

wherein Ar and R are as previously defined; or
(b) reacting a compound of the formula:



--- (V)

with a halide of the formula:

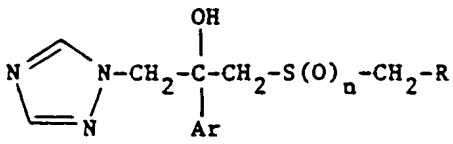
$$X—CH_2—R \qquad (VI)$$

wherein Ar and R are as previously defined and X is chloro, bromo or iodo; to give these compounds of formula (I) wherein n is 0, and oxidising to give those compounds wherein n is 1.

9. A compound of the formula (I) as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in treating fungal infections in animals, including humans.

Patentansprüche

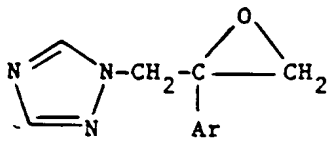
1. Verbindung der allgemeinen Formel



---(I)

worin bedeuten:
Ar Phenyl substituiert durch 1 bis 3 Substituenten, wobei jeder Substituent unabhängig Halogen oder CF_3 ist;
n 0 oder 1 und
R Phenyl oder Phenyl substituiert durch 1 bis 3 Substituenten, wobei jeder Substituent unabhängig Halogen, CF_3, C_1—C_4-Alkoxy, C_2—C_5-Alkoxycarbonyl oder C_1—C_4-Alkylthio ist; oder eine 5- oder 6-gliedrige aromatische heterocyclische Gruppe verbunden über ein Ringkohlenstoffatom und gegebenenfalls substituiert durch eine oder mehrere Halogen-, CF_3, C_1—C_4-Alkyl-, C_1—C_4-Alkoxy, Amino-, Mono- oder Di-(C_1—C_4-Alkyl)amino-, C_2—C_5-Alkanoylamino-, Hydroxy- oder Thio-Gruppen,
und Salzformen davon.

2. Verbindung nach Anspruch 1, worin Ar Mono- oder Dihalophenyl bedeutet.
3. Verbindung nach Anspruch 2, worin Ar 2,4-Dichlorophenyl bedeutet.
4. Verbindung nach einem der Ansprüche 1 bis 3, worin n 0 ist.
5. Verbindung nach Anspruch 1, worin R eine 2-Pyridyl-, 1-Methyl-2-imidazolyl-, 2-Amino-4-thiazolyl- oder 1-Methyl-5-tetrazolyl-Gruppe bedeutet.
6. Eine Verbindung nach Anspruch 1, worin die Verbindung ist:
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-pyridylmethylthio)propyl]-1,2,4-triazol,
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-2-imidazolylmethylthio)propyl]-1,2,4-triazol,
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(2-amino-4-thiazolylmethylthio)propyl]-1,2,4-triazol, oder
1-[2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1-methyl-5-tetrazolylmethylthio)propyl]-1,2,4-triazol.
7. Pharmazeutische Zusammensetzung umfassend eine Verbindung nach einem der Ansprüche 1 bis 6 oder ein pharmazeutisch annehmbares Salz davon, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
8. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, umfassend
(a) Umsetzen einer Verbindung der Formel

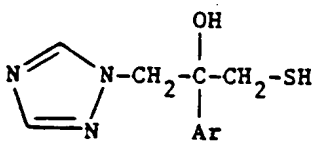


--- (II)

mit einem Thiol der Formel

$$R—CH_2—SH \qquad (III)$$

worin Ar und R die obige Bedeutung haben; oder
(b) Umsetzen einer Verbindung der Formel



--- (V)

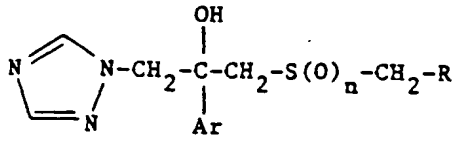
mit einem Halogenid der Formel

$$X—CH_2—R \qquad (VI)$$

worin Ar und R die obige Bedeutung haben und X Chlor, Brom oder Jod darstellt, zur Herstellung der Verbindungen der Formeln (I); in welcher n gleich 0 ist und Oxidieren zur Herstellung von Verbindungen, worin n gleich 1 ist.
9. Verbindung der Formel (I) nach einem der Ansprüche 1 bis 6 oder ein pharmazeutisch annehmbares Salz oder eine pharmazeutische Zusammensetzung davon zur Verwendung bei der Behandlung von Pilzinfektionen in Lebewesen, einschließlich Menschen.

Revendications

1. Composé de formule générale:



---(I)

dans laquelle
Ar est un groupe phényle substitué par de 1 à 3 substituants, identiques ou différents, choisis entre un groupe halogéno et CF_3;
n représente 0 ou 1; et
R est un groupe phényle ou phényle substitué par de 1 à 3 substituants, identiques ou différents, choisis entre un groupe halogéno, CF_3, alcoxy en C_1—C_4, alcoxycarbonyle en C_2—C_5 et alkylthio en C_1—C_4; ou un groupe hétérocyclique aromatique à 5 ou 6 chaînons reliés via un atome de carbone du cycle et, éventuellement, substitué par un ou plusieurs groupe(s) halogéno, CF_3, alkyle en C_1—C_4, alcoxy en C_1—C_4, amino, mono- ou di-(alkyl en C_1—C_4)amino, alcanoylamino en C_2—C_5, hydroxy ou thio,
et sels résultant d'un tel composé.

2. Composé selon la revendication 1, dans lequel Ar est un groupe mono- ou dihalogénophényle.

3. Composé selon la revendication 2, dans lequel Ar est un groupe 2,4-dichlorophényle.

4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel *n* représente 0.

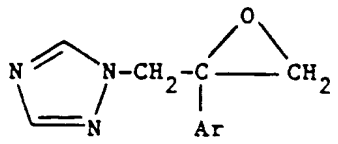
5. Composé selon la revendication 1, dans lequel R est un groupe 2-pyridyle, 1-méthyl-2-imidazolyle, 2-amino-4-thiazolyle ou 1-méthyl-5-tétrazolyle.

6. Composé selon la revendication 1, caractérisé en ce que ledit composé est le:
1-(2-(2,4-dichlorophényl)-2-hydroxy-3-(2-pyridylméthylthio)propyl)-1,2,4-triazole,
1-(2-(2,4-dichlorophényl)-2-hydroxy-3-(1-méthyl-2-imidazolylméthylthio)propyl)-1,2,4-triazole,
1-(2-(2,4-dichlorophényl)-2-hydroxy-3-(2-amino-4-thiazolyl-méthylthio)propyl)-1,2,4-triazole, ou
1-(2-(2,4-dichlorophényl)-2-hydroxy-3-(1-méthyl-5-tétrazolylméthylthio)propyl)-1,2,4-triazole.

7. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 6, ou un sel pharmaceutiquement acceptable d'une tel composé avec un diluant ou un véhicule pharmaceutiquement acceptable.

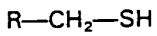
8. Procédé de préparation d'un composé de formule (I) selon la revendication 1 qui consiste:

(a) à faire réagir un composé de formule:



--- (II)

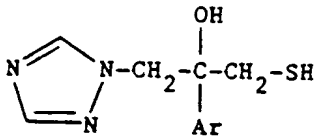
avec un thiol de formule:



(III)

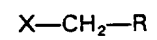
dans laquelle Ar et R sont tels que définis ci-dessus; ou

(b) à faire réagir un composé de formule:



--- (V)

avec un halogénure de formule:



(VI)

dans laquelle Ar et R sont tels que définis précédemment et X est un groupe chloro, bromo ou iodo; pour donner les composés de formule (I) dans lesquels *n* représente 0, et à les oxyder pour donner les composés dans lesquels *n* représente 1.

9. Composé de formule (I) selon l'une quelconque des revendications 1 à 6 ou sel pharmaceutiquement acceptable ou composition pharmaceutique d'un tel composé, en vue de son application dans le traitement des infections fongiques chez les animaux, y compris l'homme.